Claims

1. A method for reducing a side effect associated with thrombolytic therapy, comprising inhibiting binding of tissue plasminogen activator (tPA) administered to a subject to a low-density lipoprotein-receptor-related protein (LRP) receptor.

2. The method of claim 1, wherein inhibiting binding of tPA to LRP comprises administering to a subject in need of such treatment an amount of an agent that reduces tissue plasminogen activator (tPA) binding to a low-density lipoprotein-receptor-related protein (LRP) receptor effective to reduce the side effect, wherein the agent is administered before, simultaneously with, or after tPA treatment.

3. The method of claim 1, wherein the side effect associated with thrombolytic therapy is cerebral hemorrhage and/or edema.

4. The method of claim 1, wherein the subject is human.

5. The method of claim 1, wherein the thrombolytic therapy is the administration of tPA.

6. The method of claim 2, wherein the agent that reduces tPA binding to a LRP receptor is administered before tPA treatment.

7. The method of claim 2, wherein the agent that reduces tPA binding to a LRP receptor is administered simultaneously with tPA treatment.

8. The method of claim 2, wherein the agent that reduces tPA binding to a LRP receptor is administered after tPA treatment.

9. The method of claim 2, wherein the administration is intravenous administration.

10. The method of claim 2, wherein the agent is an antibody or antigen-binding fragment thereof.

11. The method of claim 1, wherein the subject is suspected or known to be at risk for a condition selected from the group consisting of ischemia, hemorrhage, edema, and brain injury.

12. The method of claim 1, wherein the subject is suspected or known to have a condition selected from the group consisting of: ischemia, hemorrhage, edema, and brain injury.

13. The method of claim 1, wherein the subject is suspected or known to have had a condition selected from the group consisting of: ischemia, hemorrhage, edema, and brain injury.

14. A method for reducing a side effect associated with thrombolytic therapy, comprising inhibiting binding of urokinase plasminogen activator (uPA) administered to a subject to a urokinase plasminogen activator receptor (uPAR).

15. The method of claim 14, wherein inhibiting binding of uPA to uPAR comprises administering to a subject in need of such treatment an amount of an agent that reduces urokinase plasminogen activator (uPA) binding to a urokinase plasminogen activator receptor (uPAR) effective to reduce the side effect, wherein the agent is administered before, simultaneously with, or after uPA treatment.

16. The method of claim 14, wherein the side effect associated with thrombolytic therapy is cerebral hemorrhage and/or edema.

17. The method of claim 14, wherein the subject is human.

18. The method of claim 14, wherein the thrombolytic therapy is the administration of uPA.

19. The method of claim 15, wherein the agent that reduces uPA binding to a uPAR is administered before uPA treatment.

20. The method of claim 15, wherein the agent that reduces uPA binding to uPAR is administered simultaneously with uPA treatment.

21. The method of claim 15, wherein the agent that reduces uPA binding to a uPAR is administered after uPA treatment.

22. The method of claim 15, wherein the administration is intravenous administration.

23. The method of claim 15, wherein the agent is an antibody or antigen-binding fragment thereof.

24. The method of claim 14, wherein the subject is suspected or known to be at risk for a condition selected from the group consisting of: ischemia, hemorrhage, edema, and brain injury.

25. The method of claim 14, wherein the subject is suspected or known to have a condition selected from the group consisting of: ischemia, hemorrhage, edema, and brain injury.

26. The method of claim 14, wherein the subject is suspected or known to have had a condition selected from the group consisting of: ischemia, hemorrhage, edema and brain injury.

27. A method for reducing a side effect associated with thrombolytic therapy comprising: administering to a subject in need of such treatment an effective amount of an agent that interferes with downstream signaling cascades that lead from tissue plasminogen activator-low-density lipoprotein-receptor-related protein receptor (tPA-LRP) and/or urokinase plasminogen activator-urokinase plasminogen activator receptor (uPA-uPAR) to upregulation of matrix metalloproteinases (MMPs) and other related proteases that degrade neurovascular unit integrity.

28. The method of claim 27, wherein the side effect is cerebral hemorrhage and/or edema.

29. A method of identifying a candidate agent that modulates tissue plasminogen activator (tPA) binding to a low-density lipoprotein-receptor-related protein (LRP) receptor comprising:

contacting an LRP receptor with tPA in the presence of a candidate agent,

determining the level of binding of the LRP receptor with the tPA, and

comparing the level of binding of LRP with tPA with a control level of binding of LRP and tPA not contacted with the candidate agent as a measure of the ability of the candidate agent to modulate tPA binding to LRP receptor.

30. The method of claim 29, wherein modulate is to reduce.

31. The method of claim 29, wherein modulate is to increase.

32. The method of claim 29, wherein the tPA is labeled with a detectable label.

33. The method of claim 29, wherein the LRP receptor is labeled with a detectable label.

34. A method of identifying a candidate agent that modulates urokinase plasminogen activator (uPA) binding to a urokinase plasminogen activator receptor (uPAR) comprising:

contacting a uPAR with uPA in the presence of a candidate agent,

determining the level of binding of the uPAR with the uPA, and

comparing the level of binding of uPAR with uPA with a control level of binding of uPAR and uPA not contacted with the candidate agent as a measure of the ability of the candidate agent to modulate uPA binding to uPAR receptor.

35. The method of claim 34, wherein modulate is to reduce.

36. The method of claim 34, wherein modulate is to increase.

37. The method of claim 34, wherein the uPA is labeled with a detectable label.

38. The method of claim 34, wherein the uPAR is labeled with a detectable label.

39. A method of thrombolytic therapy comprising

administering to a subject in need of such treatment a combination of an effective amount of a thrombolytic agent and an effective amount of an inhibitor of the binding of the thrombolytic agent to its receptor, wherein the binding of the thrombolytic agent to its receptor results in an increase in matrix metalloproteinase expression.

40. The method of claim 39 wherein the thrombolytic agent is tPA and its receptor is LRP receptor.

41. The method of claim 39 wherein the thrombolytic agent is uPA and its receptor is uPAR.

42. A method of identifying a thrombolytic tissue plasminogen activator (tPA) variant with reduced binding to a low-density lipoprotein-receptor-related protein (LRP) receptor, comprising:

modifying a tPA molecule to prepare modified tPA molecules,

testing the thrombolytic activity of the modified tPA molecules,

selecting modified tPA molecules that retain thrombolytic activity (modified thrombolytic tPA molecules),

contacting an LRP receptor with the modified thrombolytic tPA molecules,

determining the level of binding of the LRP receptor with modified thrombolytic tPA molecules, and

comparing the level of binding of LRP receptor by modified thrombolytic tPA molecules with a control level of binding of LRP receptor by unmodified tPA as an indication of reduced binding of the modified thrombolytic tPA molecules to LRP receptor.

43. The method of claim 42, wherein the modification of the tPA molecule comprises one or more modifications selected from the group consisting of amino acid substitutions, amino acid deletions, and post-translational modifications.

44. A method of identifying a thrombolytic urokinase plasminogen activator (uPA) variant with reduced binding to an urokinase plasminogen activator receptor (uPAR), comprising:

modifying a uPA molecule to prepare modified uPA molecules,

testing the thrombolytic activity of the modified uPA molecules,

selecting modified uPA molecules that retain thrombolytic activity (modified thrombolytic uPA molecules),

contacting an uPAR with the modified thrombolytic uPA molecules,

determining the level of binding of the uPAR with modified thrombolytic uPA molecules, and

comparing the level of binding of uPAR by modified thrombolytic uPA molecules with a control level of binding of uPAR by unmodified uPA as an indication of reduced binding of the modified thrombolytic uPA molecules to uPAR.

45. The method of claim 44, wherein the modification of the uPA molecule comprises one or more modifications selected from the group consisting of amino acid substitutions, amino acid deletions, and post-translational modifications.